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15

16 **UNITED STATES DISTRICT COURT**

17 **DISTRICT OF NEVADA**

18  
19 BAYER SCHERING PHARMA AG and  
20 BAYER HEALTHCARE  
PHARMACEUTICALS INC.,

21 Plaintiffs,

22 vs.

23 SANDOZ, INC.

24 Defendant.  
25  
26  
27

Case No. 2:08-cv-

**COMPLAINT FOR PATENT  
INFRINGEMENT**

**RELATED TO CASE NO. 2:07-cv-01472-  
KJD-GWF**

**JURY DEMAND**

1 Plaintiffs Bayer Schering Pharma AG and Bayer HealthCare Pharmaceuticals Inc. bring  
2 this Complaint for patent infringement against Defendant Sandoz, Inc. and allege as follows:

### 3 JURISDICTION AND VENUE

4 1. This action arises under the patent laws of the United States of America. This  
5 Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

6 2. Defendant has consented to personal jurisdiction in Nevada for the purposes of this  
7 action. Furthermore, upon information and belief, Defendant has continuous and systematic  
8 contacts with Nevada.

9 3. Venue is proper under 28 U.S.C. § 1391(b) and (c), and § 1400(b). Furthermore,  
10 Defendant has consented to venue in this district for the purposes of this action.

### 11 PARTIES

12 4. Plaintiff Bayer Schering Pharma AG (“Bayer Schering”), formerly known as  
13 Schering AG, is a corporation organized and existing under the laws of the Federal Republic of  
14 Germany, having a principal place of business at Müllerstrasse 178, 13353 Berlin, Germany.

15 5. Plaintiff Bayer HealthCare Pharmaceuticals Inc. (“Bayer HealthCare”), formerly  
16 known as Berlex, Inc., is a corporation organized and existing under the laws of the State of  
17 Delaware, having a principal place of business at 340 Changebridge Road, P.O. Box 1000,  
18 Montville, New Jersey 07045-1000.

19 6. On information and belief, Defendant Sandoz, Inc. (“Sandoz”) is a corporation  
20 organized and existing under the laws of the State of Colorado, having a principal place of  
21 business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540. Sandoz develops,  
22 manufactures and markets generic pharmaceutical products.

### 23 STATEMENT OF RELATED CASE

24 7. This action is related to Case No. 2:07-cv-01472-KJD-GWF because it involves the  
25 identical patents-in-suit and identical theories of patent infringement.

### 26 BACKGROUND

27 8. Bayer HealthCare is the holder of approved New Drug Application (“NDA”) No.  
28 21-676, for YAZ® tablets, which contain as active ingredients micronized drospirenone and

micronized 17 $\alpha$  -ethinylestradiol. YAZ® tablets have been approved by the United States Food and Drug Administration (“FDA”) for (a) the prevention of pregnancy in women who elect to use an oral contraceptive; (b) the treatment of acne; and (c) premenstrual dysphoric disorder (“PMDD”). YAZ® tablets are sold in the United States by Bayer HealthCare as a 28-day oral contraceptive regimen that contains 24 tablets comprising 3 mg of micronized drospirenone and 0.02 mg of micronized 17 $\alpha$  -ethinylestradiol plus 4 placebo tablets.

9. On information and belief, Sandoz submitted to the FDA an Abbreviated New Drug Application (“ANDA”) under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of a generic version of Bayer HealthCare’s YAZ® tablets. On information and belief, the FDA has assigned this Sandoz ANDA the number 79-221.

10. On information and belief, the composition of the product that is the subject of Sandoz’s ANDA contains 3 mg of drospirenone and 0.02 mg of 17 $\alpha$  -ethinylestradiol in tablet form for oral contraception in a human female.

11. On information and belief, Sandoz’s ANDA seeks approval of a 28-day oral contraceptive regimen that contains 24 tablets comprising 3 mg drospirenone and 0.02 mg 17 $\alpha$  – ethinylestradiol plus 4 placebo tablets (hereinafter, “Sandoz’s ANDA product”).

12. On information and belief, on or about June 19, 2008, Sandoz sent a Notice Letter to Plaintiffs Bayer Schering and Bayer HealthCare, purporting to comply with the provisions of 21 U.S.C. § 355(j)(2)(B) and the FDA regulations relating thereto. Plaintiff Bayer HealthCare received the Notice Letter on or about June 23, 2008. Plaintiff Bayer Schering received the Notice Letter on or about July 2, 2008.

### PATENTS-IN-SUIT

13. United States Reissue Patent No. 37,564 (“the ‘564 reissue patent”) is attached to the Complaint as Exhibit 1. Inventors Jürgen Spona, Bernd Düsterberg, and Frank Lüdicke filed their application for this patent on February 15, 2000. The ‘564 reissue patent was issued February 26, 2002. Bayer Schering is the current owner of the ‘564 reissue patent.

14. United States Reissue Patent No. 37,838 (“the ‘838 reissue patent”) is attached to

1 the Complaint as Exhibit 2. Inventors Jürgen Spona, Bernd Düsterberg, and Frank Lüdicke filed  
 2 their application for this patent on February 15, 2000. The '838 reissue patent was issued  
 3 September 10, 2002. Bayer Schering is the current owner of the '838 reissue patent.

4 **COUNT ONE: CLAIM FOR PATENT INFRINGEMENT OF**  
 5 **UNITED STATES REISSUE PATENT NO. 57,564**

6 15. Plaintiffs incorporate each of the preceding paragraphs of this Complaint as if fully  
 7 set forth here.

8 16. On information and belief, Sandoz's ANDA product infringes one or more claims  
 9 of the '564 reissue patent.

10 17. The '564 reissue patent covers Bayer HealthCare's YAZ® tablets and has been  
 11 listed for the product in the FDA *Approved Drug Products with Therapeutic Equivalence*  
 12 *Evaluations* ("the Orange Book").

13 18. On information and belief, Sandoz submitted its ANDA to the FDA for the purpose  
 14 of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale and/or  
 15 importation of Sandoz's ANDA product before the expiration of the '564 reissue patent.

16 19. On information and belief, Sandoz made and included in its ANDA a certification  
 17 under 21 U.S.C. § 355 (j)(2)(A)(vii)(IV) asserting that, in its opinion, the '564 reissue patent is  
 18 invalid.

19 20. In its Notice Letter, Sandoz did not allege non-infringement of the claims of the  
 20 '564 reissue patent.

21 21. By filing its ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval  
 22 to engage in the commercial manufacture, use, offer for sale, sale and/or importation of its ANDA  
 23 product before the expiration of the '564 reissue patent, Sandoz has committed an act of  
 24 infringement under 35 U.S.C. § 271(e)(2).

25 22. Further, on information and belief, the actual commercial manufacture, use, offer  
 26 for sale, sale and/or importation of Sandoz's ANDA product will infringe one or more claims of  
 27 the '564 reissue patent.

28 23. Plaintiffs Bayer Schering and Bayer HealthCare are entitled to the relief provided

1 by 35 U.S.C. § 271(e)(4), including an Order of this Court that the effective date of any approval  
 2 relating to Sandoz's ANDA shall be a date which is not earlier than June 30, 2014, the current  
 3 expiration date of the '564 reissue patent, or any later date of exclusivity to which Plaintiffs  
 4 become entitled. Further, Bayer Schering and Bayer HealthCare are entitled to an award of treble  
 5 damages for any commercial sale or use of Sandoz's ANDA product, and any act committed by  
 6 Sandoz with respect to the subject matter claimed in the '564 reissue patent that is not within the  
 7 limited exclusions of 35 U.S.C. § 271(e)(1).

8 24. On information and belief, when Sandoz filed its ANDA, it was aware of the '564  
 9 reissue patent and was aware that the filing of its ANDA with the request for its approval prior to  
 10 the expiration of the '564 reissue patent constituted an act of infringement of the '564 reissue  
 11 patent.

12 **COUNT TWO: CLAIM FOR PATENT INFRINGEMENT**  
 13 **OF UNITED STATES REISSUE PATENT NO. 37,838**

14 25. Plaintiffs incorporate paragraphs 1 - 14 of this Complaint as if fully set forth here.

15 26. On information and belief, Sandoz's ANDA product infringes one or more claims  
 16 of the '838 reissue patent.

17 27. The '838 reissue patent covers Bayer HealthCare's YAZ® tablets and has been  
 18 listed for the product in the FDA *Approved Drug Products with Therapeutic Equivalence*  
 19 *Evaluations* ("the Orange Book").

20 28. On information and belief, Sandoz submitted its ANDA to the FDA for the purpose  
 21 of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale and/or  
 22 importation of Sandoz's ANDA product before the expiration of the '838 reissue patent.

23 29. On information and belief, Sandoz made and included in its ANDA a certification  
 24 under 21 U.S.C. § 355 (j)(2)(A)(vii)(IV) asserting that, in its opinion, the '838 reissue patent is  
 25 invalid.

26 30. In its notice letter, Sandoz did not allege non-infringement of the '838 reissue  
 27 patent's claims.

28 31. By filing its ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval

1 to engage in the commercial manufacture, use, offer for sale, sale and/or importation of its ANDA  
 2 product before the expiration of the '838 reissue patent, Sandoz has committed an act of  
 3 infringement under 35 U.S.C. § 271(e)(2).

4 32. Further, on information and belief, the actual commercial manufacture, use, offer  
 5 for sale, sale and/or importation of Sandoz's ANDA product will also infringe one or more claims  
 6 of the '838 reissue patent.

7 33. Plaintiffs Bayer Schering and Bayer HealthCare are entitled to the relief provided  
 8 by 35 U.S.C. § 271(e)(4), including an Order of this Court that the effective date of any approval  
 9 relating to Sandoz's ANDA shall be a date which is not earlier than June 30, 2014, the current  
 10 expiration date of the '838 reissue patent, or any later date of exclusivity to which Plaintiffs  
 11 become entitled. Further, Bayer Schering and Bayer HealthCare are entitled to an award of treble  
 12 damages for any commercial sale or use of Sandoz's ANDA product, and any act committed by  
 13 Sandoz with respect to the subject matter claimed in the '838 reissue patent that is not within the  
 14 limited exclusions of 35 U.S.C. § 271(e)(1)

15 34. On information and belief, when Sandoz filed its ANDA, it was aware of the '838  
 16 reissue patent and was aware that the filing of its ANDA with the request for its approval prior to  
 17 the expiration of the '838 reissue patent constituted an act of infringement of the '838 reissue  
 18 patent.

### 19 **PRAYER FOR RELIEF**

20 **WHEREFORE**, Plaintiffs respectfully request the following relief:

21 A. Judgment that Sandoz has infringed one or more claims of the '564 reissue patent  
 22 and the '838 reissue patent by filing its ANDA relating to Sandoz's ANDA Product;

23 B. A permanent injunction restraining and enjoining Sandoz and its officers, agents,  
 24 attorneys and employees, and those acting in privity or concert with it, from engaging in the  
 25 commercial manufacture, use, offer to sell, or sale within the United States, or importation into the  
 26 United States, of Sandoz's ANDA product;

27 C. An order that the effective date of any approval of Sandoz's ANDA relating to  
 28 Sandoz's ANDA product containing drospirenone and ethinylestradiol be a date which is not

1 earlier than the expiration date of the later of the '564 reissue patent, the '838 reissue patent, or  
2 any later date of exclusivity to which Plaintiffs become entitled;

3 D. Treble damages from Sandoz for any commercial activity constituting infringement  
4 of the '564 reissue patent or the '838 reissue patent; and

5 E. Such other and further relief as the Court may deem just and proper.

6 **JURY DEMAND**

7 Plaintiffs demand a jury trial on all issues so triable.

8 DATED this 1<sup>st</sup> day of August, 2008

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24 Bayer HealthCare Pharmaceuticals Inc.  
25  
26  
27

Exhibit 1

Exhibit 1





US00RE37564E

(19) **United States**(12) **Reissued Patent****Spona et al.**(10) **Patent Number: US RE37,564 E**(45) **Date of Reissued Patent: Feb. 26, 2002**(54) **COMPOSITION FOR CONTRACEPTION**(75) Inventors: **Jürgen Spona**, Vienna (AT); **Bernd Düsterberg**, Berlin (DE); **Frank Lüdicke**, Geneva (CH)(73) Assignee: **Schering Aktiengesellschaft**, Berlin (DE)

(\*) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/503,952**(22) Filed: **Feb. 15, 2000****Related U.S. Patent Documents**

Reissue of:

(64) Patent No.: **5,824,667**  
 Issued: **Oct. 20, 1998**  
 Appl. No.: **09/742,147**  
 Filed: **Oct. 31, 1996**

U.S. Applications:

(63) Continuation of application No. 08/268,996, filed on Jun. 30, 1994, now Pat. No. 5,583,129.

(30) **Foreign Application Priority Data**

Dec. 22, 1993 (DE) ..... 43 44 462

(51) **Int. Cl.<sup>7</sup>** ..... **A61K 31/57**; A61K 31/565(52) **U.S. Cl.** ..... **514/170**(58) **Field of Search** ..... 514/170(56) **References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—Phyllis G. Spivack

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(57)

**ABSTRACT**

A combination product for oral contraception is disclosed comprising an estrogen selected from

2.0 to 6.0 mg of 17β-estradiol and

0.020 mg of ethinylestradiol;

and a gestagen selected from

[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone and

[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,

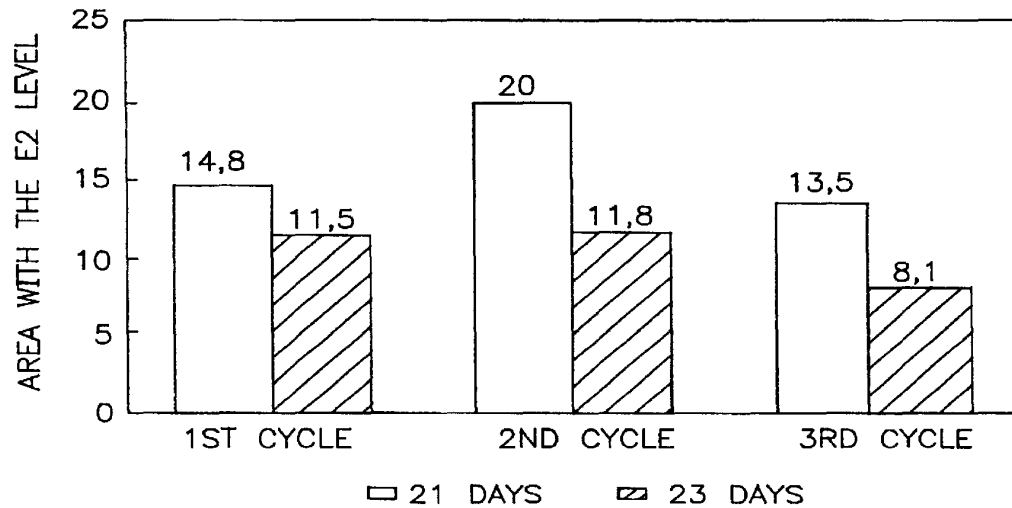
followed by 5 or 4 pill-free or sugar pill days.

**13 Claims, 1 Drawing Sheet**

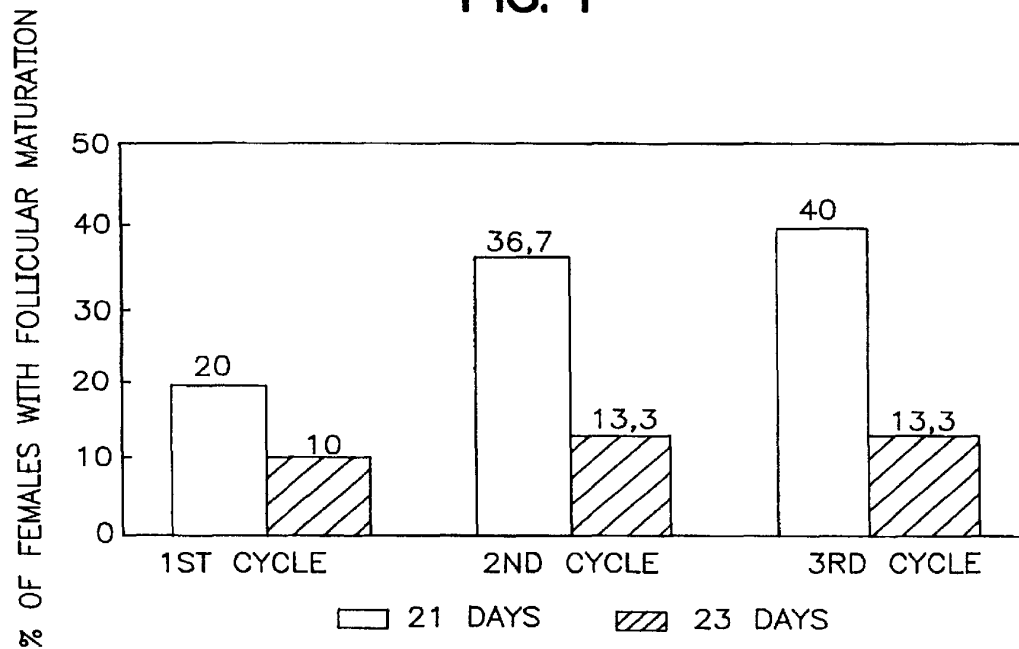
**U.S. Patent**

**Feb. 26, 2002**

**US RE37,564 E**



**FIG. 1**



**FIG. 2**

US RE37,564 E

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## COMPOSITION FOR CONTRACEPTION

**Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.**

[This] *This application is the parent of application Ser. No. 09/504,084, both filed Feb. 15, 2000, both of which are reissues of application Ser. No. 08/742,147, filed Oct. 31, 1996, now U.S. Pat. No. 5,824,667, which is a continuation of the application Ser. No. 08/268,996 filed Jun. 30, 1994, now U.S. Pat. No. 5,583,129.*

## DESCRIPTION

This invention relates to the common use of estrogen and gestagens for the production of a combination preparation for oral contraception and a corresponding pack containing this combination preparation.

Combination preparations for oral contraception are already known, for example, Femovan® [DE-PS 2 546 062] or Marvelon® [DE-OS 2 361 120]. These preparations consist of 21 active ingredient-containing (estrogen/gestagen) dosage units and 7 active ingredient-free coated tablets (sugar pills; placebos). The dose to be administered daily is uniformly high in each case (so-called single-phase preparations) and produces the desired contraceptive effect in the entire intake period and in the intake pause or during the intake of the placebos. In most preparations, a 7-day interruption of the intake of active ingredient-containing dosage units was considered necessary until quite recently to trigger a reliable withdrawal bleeding and thus to achieve a satisfactory cycle control.

Other preparations, which exhibit more than 21 dosage units containing an estrogenic and progestational active ingredient, and in which the intake pause is partially (Ijzerman, Pasquale) or completely (Kuhl) bridged over by estrogen-containing dosage units. In this case, it is possible that the synthetic estrogen ethinylestradiol otherwise contained in oral contraceptives is replaced partially or completely by a conjugated estrogen, preferably estradiol.

A combination preparation for substitution therapy and contraception for females before menopause (approximately starting from the 40th year of life) is known from EP-A-0 253 607. This combination preparation contains an estrogen from the group

17 $\beta$ -Estradiol,  
ethinylestradiol and  
mestranol

as well as a gestagen from the group

levonorgestrel,  
gestodene,  
desogestrel,  
3-ketodesogestrel and  
norethindrone.

A thus selected composition is to offset hormonal irregularities in the transition phase of premenopause and to help alleviate the symptoms caused by the hormonal changeover of the female organism in this phase. Such a composition simultaneously assures a premenopausal female the contraceptive protection still necessary at this age.

The development of new oral contraceptives for females of reproductive age before premenopause was characterized during the last twenty years above all by the reduction of the estrogen and gestagen dosages.

The reduction of the daily hormone dose was connected with the expectation to minimize the frequency of undesired

2

side effects. Epidemiological data collected in the meantime confirm the desired trend toward better compatibility of lower-dosed preparations relative to cardiovascular complications [(1.) Thorogood, M., Oral Contraceptives and Cardiovascular Disease: An Epidemiologic Overview; Pharmacoeconomics and Drug Safety, Vol. 2: 3-16 (1993); (2.) Gerstman, B. B.; Piper, J. M.; Tomita, D. K.; Ferguson, W. J.; Stadel, B. V.; Lundin, F. E.; Oral Contraceptive Estrogen Dose and the Risk of Deep Venous Thromboembolic Disease, Am. J. E., Vol. 133, No. 1, 32-36 (1991); (3.) Lidegaard, O., Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study; BMJ Vol. 306, 956-63 (1993); (4.) Vessey, M.; Mant, D.; Smith, A.; Yeates, D.; Oral contraceptives and venous thromboembolism: findings in a large prospective study; BMJ, Vol. 292, (1986); (5.) Mishell, D. R., Oral Contraception: Past, Present and Future Perspectives; Int. J. Fertil., 36 Suppl., 7-18 (1991)].

It is assumed that a correlation exists above all between the level of the estrogen dose and the incidence of cardiovascular diseases. But the maintenance of the contraceptive effectiveness stands in the way of an extreme reduction of the daily estrogen dose. Although the ovulation-inhibiting effect of the low-dosed oral contraceptives is caused mainly by the gestagenic component, the estrogenic component also makes a significant contribution to the central inhibition action and to the ovarian suppression (ovulation inhibition). Moreover, the daily estrogen dose must not fall below the minimum dose ranges, so that a satisfactory cycle control can be assured (Der Frauenarzt [The Gynecologist]; 34, 7: 793 (1993)).

The lowest estrogen dose contained in an oral contraceptive on the market at this time is 20  $\mu$ g of ethinylestradiol, combined with 150  $\mu$ g of desogestrel (Mercilon). Although the cycle control of this preparation is, as expected, somewhat poorer in comparison to preparations with a higher estrogen dose, the high acceptance rate of Mercilon indicates a small clinical relevance of this drawback. But the observation, made identically in several studies, of a lesser ovarian suppression of the preparation containing 20  $\mu$ g of ethinylestradiol represents a clinically important problem. Obviously with this very low estrogen dose, in the case of many females, the maturation of follicles, which could be detected with ultrasonic studies or hormonal studies, results [(6.) Lunell, N. O.; Carström, K.; Zador, G.; Ovulation inhibition with a combined oral contraceptive containing 20  $\mu$ g of ethinylestradiol and 250  $\mu$ g of levonorgestrel; Acta. Obstet. Gynecol. Scand. Suppl. 88: 17-21 (1979); (7.) Mall-Haefeli, M.; Werner-Zodrow, I.; Huber, P. R.; Klinische Erfahrungen mit Mercilon und Marvelon unter besonderer Berücksichtigung der Ovar-Funktion [Clinical Experience with Mercilon and Marvelon under special consideration of the ovary function]; Geburtsh. und Frauenheilk. [Obstetrics and Gynecology] 51, 35-38, Georg Thieme Verlag, Stuttgart-New York (1991); (8.) Strobel, E., Behandlung mit oralen Kontrazeptiva [Treatment with Oral Contraceptives]; Fortschr. Med. Vol. 110, No. 20 (1992); (9.) Letter to Editor, Contraception 45: 519-521 (1992); (10.) Teichmann, A. T.; Brill, K.; Can Dose Reduction of Ethinylestradiol in OCs Jeopardize Ovarian Suppression and Cycle Control? Abstract Book, VIIIth World Congress on Human Reproduction, Bali, Indonesia (1993)].

The hormone determinations performed showed that functional granulosa cells that secrete 17 $\beta$ -estradiol are involved. Each intake error in the case of females with clear ovarian activity, thus with follicular maturations, can result in a quick increase of gonadotropin production. The require-

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ments for an ovulation would thus be present. It is estimated that approximately one third of females take oral contraceptives irregularly within one year of use (Gynpress, Volume 1, No. 3, 1990). The risk of a pregnancy is therefore high especially in the case of intake errors with the 20  $\mu$ g ethinylestradiol preparations.

The object of this invention is an improved single-phase combination preparation for a female of reproductive age, who is not yet in premenopause, containing an estrogen and gestagen in each individual dosage unit, with the lowest possible estrogen content in each individual dosage unit, but also with a low total hormone content per administration cycle.

It has now been found that a pronounced ovarian suppression without frequent follicular maturations with low daily estrogen dosage, low total estrogen as well as low total hormone amount per administration cycle can be achieved by the use of a composition comprising an estrogen selected from

2.0 to 6.0 mg of 17 $\beta$ -estradiol and  
0.015 to 0.020 mg of ethinylestradiol,  
and a gestagen selected from  
0.05 to 0.075 mg of gestodene,  
0.075 to 0.125 mg of levonorgestrel,  
0.06 to 0.15 mg of desogestrel,  
0.06 to 0.15 mg of 3-ketodesogestrel,  
[0.1 to 0.3] 1 to 3 mg of drospirenone,  
[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,  
0.2 to 0.3 mg of norgestimate and  
>0.35 to 0.75 mg of norethisterone.

for the production of a form of dosage for contraception for a female of reproductive age, who has not yet reached premenopause, by administration of the form of dosage for 23 or 24 days, beginning on day one of the menstrual cycle (first day of menstrual bleeding), followed by 5 or 4 pill-free or sugar pill days, during a total of 28 days in the administration cycle.

The terms "premenopause" and "menopause" are used within the scope of this invention in the meaning of the conventional definition, see, for example, "The Controversial Climacteric," P. A. of Keep et al., Ed., MTP press (1981), e.g., p. 9.

The daily hormone dose is kept to a very low level here, while the usual 21-day intake is extended by two or three days. The remaining 5 or 4 days of a cycle are preferably bridged over by placebos, to avoid intake errors, or by 5 or 4 intake-free days.

According to a preferred embodiment of this invention, this relates to the use of a composition comprising an estrogen selected from

>2.0 to 6.0 mg of 17 $\beta$ -estradiol and  
0.020 mg of ethinylestradiol;  
and a gestagen selected from  
>0.06 to 0.075 mg of gestodene,  
>0.100 to 0.125 mg of levonorgestrel,  
>0.10 to 0.15 mg of desogestrel,  
>0.10 to 0.15 mg of 3-ketodesogestrel,  
[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone,  
[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,  
0.2 to 0.3 mg of norgestimate and  
0.50 to 0.75 mg of norethisterone

for the production of a form of dosage for contraception as described above.

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In addition, this invention relates to a combination product for oral contraception, which comprises

a) 23 or 24 dosage units, each containing an estrogen selected from

>2.0 to 6.0 mg of 17 $\beta$ -estradiol and  
0.020 mg of ethinylestradiol;  
and a gestagen selected from  
>0.06 to 0.075 mg of gestodene,  
>0.100 to 0.125 mg of levonorgestrel,  
>0.10 to 0.15 mg of desogestrel,  
>0.10 to 0.15 mg of 3-ketodesogestrel,  
[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone,  
[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,  
0.2 to 0.3 mg of norgestimate and  
0.50 to 0.75 mg of norethisterone

and

b) 5 or 4 sugar pills or other indications to show that the daily administration of 23 or 24 dosage units is to be followed by 5 or 4 pill-free or sugar pill days are to be followed.

Further embodiments according to the invention follow from the features of the subclaims.

An especially preferred combination preparation according to this invention comprises 23 dosage units, each containing 20  $\mu$ g of ethinylestradiol and 75  $\mu$ g of gestodene and 5 sugar pills or other indications to show that no dosage unit or a sugar pill is administered during the last 5 days of the menstrual cycle.

The clinical study briefly described below was performed with ethinylestradiol as estrogen and gestodene as representative of the substance class of the gestagens possible according to the invention. All possible combinations of ethinylestradiol or estradiol according to the invention in the indicated dosages with one of the selected gestagens in the indicated dosages as 23- or 24-day preparations exhibit the advantages according to the invention.

The 23-day administration of 20  $\mu$ g of ethinylestradiol in combination with 75  $\mu$ g of gestodene results, in comparison to the 21-day administration, in a stronger ovarian suppression. In a double-placebo, randomized study on healthy females with normal ovarian function, groups of 30 test subjects each received the combination preparation either once daily over 21 or 23 days as well as placebos on 7 or 5 days (to assure the double-placebo nature of the study).

The treatment began after an ovulatory, untreated preliminary cycle on the first day of the menstrual bleeding of the subsequent cycle and extended altogether over three treatment cycles. The study was concluded with an untreated follow-up cycle.

The ovarian suppression was measured based on the level of the endogenous 17 $\beta$ -estradiol level and the size of follicular structures. The results show that the 17 $\beta$ -estradiol levels with 23-day intake of the test preparation were significantly lower ( $p < 0.05$ ) in comparison to the 21-day administration (FIG. 1).

In accordance with this finding, the number of females with follicular maturations was also clearly higher in the 21-time administration relative to the 23-time administration (FIG. 2).

The intake interval extended only by two days surprisingly produces a significantly greater ovarian suppression with unchangingly low daily doses. The combination preparation according to the invention thus achieves the effectiveness previously known for preparations with a daily content of 30  $\mu$ g of ethinylestradiol, although the daily

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ethinylestradiol dose is 33% lower and also the total dose per cycle is 27% lower.

The advantages of a combination preparation for oral contraception to be administered over 23 days relative to the usual 21-day preparations with less than 30 µg of ethinylestradiol can be characterized as follows:

1. A significantly lower frequency of follicular developments in the user (maximum of 13% in females who received the 23-day preparation relative to a maximum of 40% among those who received the 21-day preparation). This means a greater contraceptive reliability of the 23-day preparation, especially in the case of previous intake errors. The danger of "breakthrough ovulations" is smaller.

2. The occurrence of large follicles of more than a 30 mm diameter is extremely rare. The development of ovarian cysts is improbable with the 23-day preparation in comparison to the 21-day preparation.

3. The recruitment of dominant follicles is suppressed in the shortened intake-free pause.

4. The endogenous 17β-estradiol levels are suppressed easily controllably in the case of the majority of the users of the 23-day preparation. Clinical symptoms such as breast tenderness, premenstrual syndrome and menstrual disorders, which can be attributed to increased and greatly fluctuating estrogen levels, are observed with the 23-day preparation with clearly lower frequency.

In summary, an intake, extended by two (or three) days, of preparations containing 20 µg of ethinylestradiol in each daily dosage unit can produce the above-mentioned advantages, without the daily dose having to be raised to the previously largely used level of 30 µg of ethinylestradiol.

The formulation of an estrogen and gestagen for the use according to the invention or for a combination preparation according to the invention takes place completely analogously as it is already known for usual oral contraceptives with 21-day intake period of the active ingredients, such as, for example, Femovan® (ethinylestradiol/gestodene) or Microgynon® (ethinylestradiol/levonorgestrel).

A pack containing a combination preparation according to the invention is also designed analogously to packs for already known oral contraceptives on the market with the variation that instead of the usual 21 dosage units containing the active components, now 23 or 24 such dosage units and 5 or 4 sugar pills are present or else contain other suitable indications that 5 or 4 days are to be bridged over until continuation of the intake of active ingredient-containing dosage units.

Moreover, reference is made to the statements made in EP-A 0 253 607, especially also to the statements there for determination of equivalent amounts of ethinylestradiol and 17β-estradiol, on the one hand, and various gestagens, such as levonorgestrel, desogestrel, 3-ketodesogestrel and gestodene, on the other hand.

For further details for the determination of dose equivalents of various gestagenic active ingredients, reference is made to "Probleme der Dosisfindung: Sexualhormone" [Problems of Dose-Finding: Sex Hormones]; F. Neumann et al. in "Arzneimittelforschung" (Pharmaceutical Agent Research) 27, 2a, 296-318 (1977), as well as to "Aktuelle Entwicklungen in der hormonalen Kontrazeption" [Current Developments in Hormonal Contraception]; H. Kuhl in Gynäkologe" [Gynecologist] 25: 231-240 (1992).

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Area with the 17β-estradiol level in groups of 30 females, who are treated with an oral contraceptive (75 µg of gestodene+20 µg of ethinylestradiol) in 21- or 23-day administration interval over three cycles.

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FIG. 2: Number of females in %, who showed follicular developments (>13 mm diameter) with 21- or 23-day treatment with an oral contraceptive (75 µg of gestodene+20 µg of ethinylestradiol).

We claim:

1. A combination product for oral contraception, comprising

(a) 23 or 24 dosage units, each containing an estrogen selected from  
>2.0 to 6.0 mg of 17β-estradiol and  
0.020 mg of ethinylestradiol;

and a gestagen selected from

[0.25 to 0.30] 2.5 to 3.0 mg of drospirenone and  
[0.1 to 0.2] 1 to 2 mg of cyproterone acetate,

and

(b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units respectively, is to be followed by 5 or 4, respectively pill-free or placebo pill days.

2. A combination preparation for oral contraception according to claim 1, wherein the estrogen is ethinylestradiol.

3. A combination preparation of claim 2, wherein the gestagen is cyproterone acetate.

4. A combination preparation of claim 2, wherein the gestagen is drospirenone.

5. A combination preparation according to claim 1, wherein the estrogen is present in a dose of 20 µg of ethinylestradiol or an equivalent dose of 17β-estradiol and the gestagen is present in a dose equivalent to 75 µg of gestodene.

6. A combination preparation according to claim 1, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.

7. A combination preparation according to claim 1, which comprises 23 dosage units, each containing 20 µg of ethinylestradiol and a dose of cyproterone acetate or drospirenone equivalent to 75 µg of gestodene and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.

8. A combination preparation of claim 1, wherein the estrogen is 17β-estradiol.

9. A combination preparation of claim 8, wherein the gestagen is cyproterone acetate.

10. A combination preparation of claim 8, wherein the gestagen is drospirenone.

11. A combination preparation of claim 4, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 5 days of the menstrual cycle.

12. A combination preparation of claim 4, which comprises 24 dosage units and 4 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 4 days of the menstrual cycle.

13. A combination product for oral contraception, comprising

(a) 23 or 24 daily dosage units, each containing  
0.020 mg of ethinylestradiol, and  
2.5 to 3.0 mg of drospirenone,  
and

(b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units, respectively, is to be followed by 5 or 4, respectively, pill-free or placebo pill days,

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*wherein each of the dosage units containing drospirenone contains the same amount of drospirenone.*

*14. A combination preparation of claim 13, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 5 days of the menstrual cycle.*

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*15. A combination preparation of claim 13, which comprises 24 dosage units and 4 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 4 days of the menstrual cycle.*

\* \* \* \* \*

## Exhibit 2

## Exhibit 2





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(19) **United States**(12) **Reissued Patent****Spona et al.**(10) **Patent Number: US RE37,838 E**(45) **Date of Reissued Patent: \*Sep. 10, 2002**(54) **COMPOSITION FOR CONTRACEPTION**(75) Inventors: **Jürgen Spona**, Vienna (AT); **Bernd Düsterberg**, Berlin (DE); **Frank Lüdicke**, Geneva (CH)(73) Assignee: **Schering Aktiengesellschaft** (DE)

(\*) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/504,084**(22) Filed: **Feb. 15, 2000****Related U.S. Patent Documents**

Reissue of:

(64) Patent No.: **5,824,667**  
 Issued: **Oct. 20, 1998**  
 Appl. No.: **08/742,147**  
 Filed: **Oct. 31, 1996**

U.S. Applications:

(63) Continuation of application No. 08/268,996, filed on Jun. 30, 1994, now Pat. No. 5,583,129.

(30) **Foreign Application Priority Data**

Dec. 22, 1993 (DE) ..... 4344462

(51) **Int. Cl.<sup>7</sup>** ..... **A61K 31/56; A61K 31/57**(52) **U.S. Cl.** ..... **514/170**(58) **Field of Search** ..... 514/170(56) **References Cited****U.S. PATENT DOCUMENTS**

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German Pharmacopeia, 9th Edition, 1986—English Translation.

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*Primary Examiner*—Phyllis G. Spivack(57) **ABSTRACT**

A combination product for oral contraception is disclosed comprising an estrogen selected from 2.0 to 6.0 mg of 17β-estradiol and 0.020 mg of ethinylestradiol; and a gestagen selected from [0.25 to 0.30 mg of] drospirenone and [0.1 to 0.2 mg of] cyproterone acetate, followed by 5 or 4 pill-free or sugar pill days.

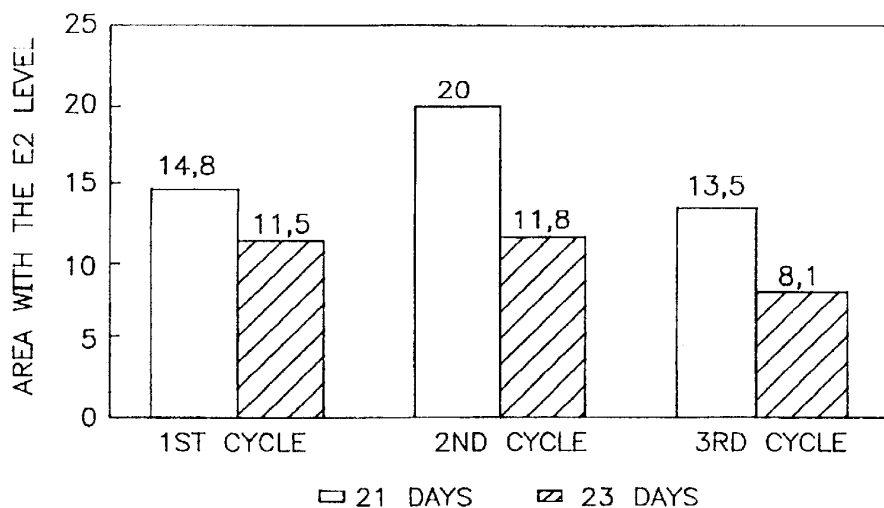
**15 Claims, 1 Drawing Sheet**



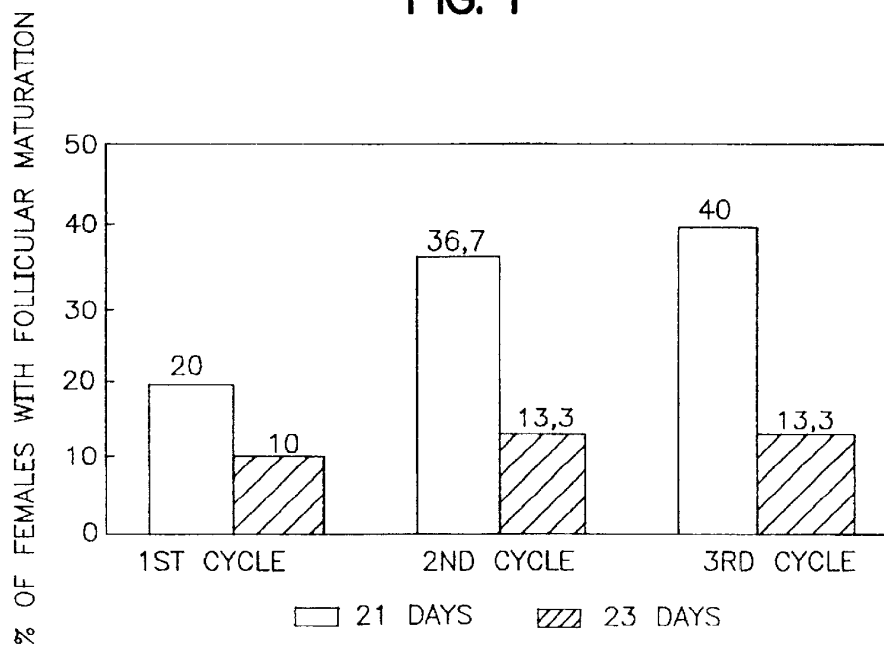
**U.S. Patent**

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**FIG. 1**



**FIG. 2**

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## COMPOSITION FOR CONTRACEPTION

**Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.**

[This] *This reissue application is a continuation of Ser. No. 09/503,952 now RE37564, filed on even date; application Ser. No. 742,147, filed Oct. 31, 1996, now U.S. Pat. No. 5,824,667, which is a continuation of the application Ser. No. 08/268,996 filed Jun. 30, 1994, now U.S. Pat. No. 5,583,129.*

## DESCRIPTION

This invention relates to the common use of estrogens and gestagens for the production of a combination preparation for oral contraception and a corresponding pack containing this combination preparation.

Combination preparations for oral contraception are already known, for example, Femovan® [DE-PS 2 546 062] or Marvelon® [DE-OS 2 361 120]. These preparations consist of 21 active ingredient-containing (estrogen/gestagen) dosage units and 7 active ingredient-free coated tablets (sugar pills; placebos). The dose to be administered daily is uniformly high in each case (so-called single-phase preparations) and produces the desired contraceptive effect in the entire intake period and in the intake pause or during the intake of the placebos. In most preparations, a 7-day interruption of the intake of active ingredient-containing dosage units was considered necessary until quite recently to trigger a reliable withdrawal bleeding and thus to achieve a satisfactory cycle control.

Other preparations, which exhibit more than 21 dosage units containing an estrogenic and progestational active ingredient, and in which the intake pause is partially (Ijzerman, Pasquale) or completely (Kuhl) bridged over by estrogen-containing dosage units. In this case, it is possible that the synthetic estrogen ethinylestradiol otherwise contained in oral contraceptives is replaced partially or completely by a conjugated estrogen, preferably estradiol.

A combination preparation for substitution therapy and contraception for females before menopause (approximately starting from the 40th year of life) is known from EP-A-0 253 607. This combination preparation contains an estrogen from the group

17 $\beta$ -Estradiol,  
ethinylestradiol and  
mestranol

as well as a gestagen from the group

levonorgestrel,  
gestodene,  
desogestrel,  
3-ketodesogestrel and  
norethindrone.

A thus selected composition is to offset hormonal irregularities in the transition phase of premenopause and to help alleviate the symptoms caused by the hormonal changeover of the female organism in this phase. Such a composition simultaneously assures a premenopausal female the contraceptive protection still necessary at this age.

The development of new oral contraceptives for females of reproductive age before premenopause was characterized during the last twenty years above all by the reduction of the estrogen and gestagen dosages.

The reduction of the daily hormone dose was connected with the expectation to minimize the frequency of undesired

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side effects. Epidemiological data collected in the meantime confirm the desired trend toward better compatibility of lower-dosed preparations relative to cardiovascular complications [(1.) Thorogood, M., Oral Contraceptives and Cardiovascular Disease: An Epidemiologic Overview; Pharmacoeconomics and Drug Safety, Vol. 2: 3-16 (1993); (2.) Gerstman, B. B.; Piper, J. M.; Tomita, D. K.; Ferguson, W. J.; Stadel, B. V.; Lundin, F. E.; Oral Contraceptive Estrogen Dose and the Risk of Deep Venous Thromboembolic Disease, Am. J. E., Vol. 133, No. 1, 32-36 (1991); (3.) Lidegaard, O., Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study; BMJ Vol. 306, 956-63 (1993); (4.) Vessey, M.; Mant, D.; Smith, A.; Yeates, D.; Oral contraceptives and venous thromboembolism: findings in a large prospective study; BMJ, Vol. 292, (1986); (5.) Mishell, D. R., Oral Contraception: Past, Present and Future Perspectives; Int. J. Fertil., 36 Suppl., 7-18 (1991)].

It is assumed that a correlation exists above all between the level of the estrogen dose and the incidence of cardiovascular diseases. But the maintenance of the contraceptive effectiveness stands in the way of an extreme reduction of the daily estrogen dose. Although the ovulation-inhibiting effect of the low-dosed oral contraceptives is caused mainly by the gestagenic component, the estrogenic component also makes a significant contribution to the central inhibition action and to the ovarian suppression (ovulation inhibition). Moreover, the daily estrogen dose must not fall below the minimum dose ranges, so that a satisfactory cycle control can be assured (Der Frauenarzt [The Gynecologist]; 34, 7: 793 (1993)).

The lowest estrogen dose contained in an oral contraceptive on the market at this time is 20  $\mu$ g of ethinylestradiol, combined with 150  $\mu$ g of desogestrel (Mercilon). Although the cycle control of this preparation is, as expected, somewhat poorer in comparison to preparations with a higher estrogen dose, the high acceptance rate of Mercilon indicates a small clinical relevance of this drawback. But the observation, made identically in several studies, of a lesser ovarian suppression of the preparation containing 20  $\mu$ g of ethinylestradiol represents a clinically important problem. Obviously with this very low estrogen dose, in the case of many females, the maturation of follicles, which could be detected with ultrasonic studies or hormonal studies, results [(6.) Lunell, N. O.; Carlström, K.; Zador, G.; Ovulation inhibition with a combined oral contraceptive containing 20  $\mu$ g of ethinylestradiol and 250  $\mu$ g of levonorgestrel; Acta. Obstet. Gynecol. Scand. Suppl. 88: 17-21 (1979); (7.) Mall-Haefeli, M.; Werner-Zodrow, I.; Huber, P. R.; Klinische Erfahrungen mit Mercilon und Marvelon unter besonderer Berücksichtigung der Ovar-Funktion [Clinical Experience with Mercilon and Marvelon under special consideration of the ovary function]; Geburtsh. und Frauenheilk. [Obstetrics and Gynecology] 51, 35-38, Georg Thieme Verlag, Stuttgart-New York (1991); (8.) Strobel, E., Behandlung mit oralen Kontrazeptiva [Treatment with Oral Contraceptives]; Fortschr. Med. Vol. 110, No. 20 (1992); (9.) Letter to Editor, Contraception 45: 519-521 (1992); (10.) Teichmann, A. T.; Brill, K.; Can Dose Reduction of Ethinylestradiol in OCs Jeopardize Ovarian Suppression and Cycle Control? Abstract Book, VIIth World Congress on Human Reproduction, Bali, Indonesia (1993)].

The hormone determinations performed showed that functional granulosa cells that secrete 17 $\beta$ -estradiol are involved. Each intake error in the case of females with clear ovarian activity, thus with follicular maturations, can result in a quick increase of gonadotropin production. The require-

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ments for an ovulation would thus be present. It is estimated that approximately one third of females take oral contraceptives irregularly within one year of use (Gynpress, Volume 1, No. 3, 1990). The risk of a pregnancy is therefore high especially in the case of intake errors with the 20  $\mu$ g ethinylestradiol preparations.

The object of this invention is an improved single-phase combination preparation for a female of reproductive age, who is not yet in premenopause, containing an estrogen and gestagen in each individual dosage unit, with the lowest possible estrogen content in each individual dosage unit, but also with a low total hormone content per administration cycle.

It has now been found that a pronounced ovarian suppression without frequent follicular maturations with low daily estrogen dosage, low total estrogen as well as low total hormone amount per administration cycle can be achieved by the use of a composition comprising an estrogen selected from

2.0 to 6.0 mg of 17 $\beta$ -estradiol and  
0.015 to 0.020 mg of ethinylestradiol;  
and a gestagen selected from  
0.05 to 0.075 mg of gestodene,  
0.075 to 0.125 mg of levonorgestrel,  
0.06 to 0.15 mg of desogestrel,  
0.06 to 0.15 mg of 3-ketodesogestrel,  
[0.1 to 0.3 mg of] drospirenone,  
[0.1 to 0.2 mg of] cyproterone acetate,  
0.2 to 0.3 mg of norgestimate and  
>0.35 to 0.75 mg of norethisterone.

for the production of a form of dosage for contraception for a female of reproductive age, who has not yet reached premenopause, by administration of the form of dosage for 23 or 24 days, beginning on day one of the menstrual cycle (first day of menstrual bleeding), followed by 5 or 4 pill-free or sugar pill days, during a total of 28 days in the administration cycle.

The terms "premenopause" and "menopause" are used within the scope of this invention in the meaning of the conventional definition, see, for example, "The Controversial Climacteric," P. A. of Keep et al., Ed., MTP press (1981), e.g., p. 9.

The daily hormone dose is kept to a very low level here, while the usual 21-day intake is extended by two or three days. The remaining 5 or 4 days of a cycle are preferably bridged over by placebos, to avoid intake errors, or by 5 or 4 intake-free days.

According to a preferred embodiment of this invention, this relates to the use of a composition comprising an estrogen selected from

>2.0 to 6.0 mg of 17 $\beta$ -estradiol and  
0.020 mg of ethinylestradiol;  
and a gestagen selected from  
>0.06 to 0.075 mg of gestodene,  
>0.100 to 0.125 mg of levonorgestrel,  
>0.10 to 0.15 mg of desogestrel,  
>0.10 to 0.15 mg of 3-ketodesogestrel,  
0.25 to 0.30 mg of drospirenone,  
[0.1 to 0.2 mg of] cyproterone acetate,  
0.2 to 0.3 mg of norgestimate and  
0.50 to 0.75 mg of norethisterone

for the production of a form of dosage for contraception as described above.

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In addition, this invention relates to a combination product for oral contraception, which comprises

a) 23 or 24 dosage units, each containing an estrogen selected from  
>2.0 to 6.0 mg of 17 $\beta$ -estradiol and  
0.020 mg of ethinylestradiol;  
and a gestagen selected from  
>0.06 to 0.075 mg of gestodene,  
>0.100 to 0.125 mg of levonorgestrel,  
>0.10 to 0.15 mg of desogestrel,  
>0.10 to 0.15 mg of 3-ketodesogestrel,  
[0.25 to 0.30 mg of] drospirenone,  
[0.1 to 0.2 mg of] cyproterone acetate,  
0.2 to 0.3 mg of norgestimate and  
0.50 to 0.75 mg of norethisterone

and  
b) 5 or 4 sugar pills or other indications to show that the daily administration of 23 or 24 dosage units is to be followed by 5 or 4 pill-free or sugar pill days are to be followed.

Further embodiments according to the invention follow from the features of the subclaims.

An especially preferred combination preparation according to this invention comprises 23 dosage units, each containing 20  $\mu$ g of ethinylestradiol and 75  $\mu$ g of gestodene and 5 sugar pills or other indications to show that no dosage unit or a sugar pill is administered during the last 5 days of the menstrual cycle.

The clinical study briefly described below was performed with ethinylestradiol as estrogen and gestodene as representative of the substance class of the gestagens possible according to the invention. All possible combinations of ethinylestradiol or estradiol according to the invention in the indicated dosages with one of the selected gestagens in the indicated dosages as 23- or 24-day preparations exhibit the advantages according to the invention.

The 23-day administration of 20  $\mu$ g of ethinylestradiol in combination with 75  $\mu$ g of gestodene results, in comparison to the 21-day administration a stronger ovarian suppression. In a double-placebo, randomized study on healthy females with normal ovarian function, groups of 30 test subjects each received the combination preparation either once daily over 21 or 23 days as well as placebos on 7 or 5 days (to assure the double-placebo nature of the study).

The treatment began after an ovulatory, untreated preliminary cycle on the first day of the menstrual bleeding of the subsequent cycle and extended altogether over three treatment cycles. The study was concluded with an untreated follow-up cycle.

The ovarian suppression was measured based on the level of the endogenous 17 $\beta$ -estradiol level and the size of follicular structures. The results show that the 17 $\beta$ -estradiol levels with 23-day intake of the test preparation were significantly lower ( $p < 0.05$ ) in comparison to the 21-day administration (FIG. 1).

In accordance with this finding, the number of females with follicular maturations was also clearly higher in the 21-time administration relative to the 23-time administration (FIG. 2).

The intake interval extended only by two days surprisingly produces a significantly greater ovarian suppression with unchangingly low daily doses. The combination preparation according to the invention thus achieves the effectiveness previously known for preparations with a daily content of 30  $\mu$ g of ethinylestradiol, although the daily ethinylestradiol dose is 33% lower and also the total dose per cycle is 27% lower.

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The advantages of a combination preparation for oral contraception to be administered over 23 days relative to the usual 21-day preparations with less than 30  $\mu\text{g}$  of ethinylestradiol can be characterized as follows:

1. A significantly lower frequency of follicular developments in the user (maximum of 13% in females who received the 23-day preparation relative to a maximum of 40% among those who received the 21-day preparation). This means a greater contraceptive reliability of the 23-day preparation, especially in the case of previous intake errors. The danger of "breakthrough ovulations" is smaller.
2. The occurrence of large follicles of more than a 30 mm diameter is extremely rare. The development of ovarian cysts is improbable with the 23-day preparation in comparison to the 21-day preparation.
3. The recruitment of dominant follicles is suppressed in the shortened intake-free pause.
4. The endogenous  $17\beta$ -estradiol levels are suppressed easily controllably in the case of the majority of the users of the 23-day preparation. Clinical symptoms such as breast tenseness, premenstrual syndrome and menstrual disorders; which can be attributed to increased and greatly fluctuating estrogen levels, are observed with the 23-day preparation with clearly lower frequency.

In summary, an intake, extended by two (or three) days, of preparations containing 20  $\mu\text{g}$  of ethinylestradiol in each daily dosage unit can produce the above-mentioned advantages, without the daily dose having to be raised to the previously largely used level of 30  $\mu\text{g}$  of ethinylestradiol.

The formulation of an estrogen and gestagen for the use according to the invention or for a combination preparation according to the invention takes place completely analogously as it is already known for usual oral contraceptives with 21-day intake period of the active ingredients, such as, for example, Femovang (ethinylestradiol/gestodene) or Microgynon® (ethinylestradiol/levonorgestrel).

A pack containing a combination preparation according to the invention is also designed analogously to packs for already known oral contraceptives on the market with the variation that instead of the usual 21 dosage units containing the active components, now 23 or 24 such dosage units and 5 or 4 sugar pills are present or else contain other suitable indications that 5 or 4 days are to be bridged over until continuation of the intake of active ingredient-containing dosage units.

Moreover, reference is made to the statements made in EP-A 0 253 607, especially also to the statements there for determination of equivalent amounts of ethinylestradiol and  $17\beta$ -estradiol, on the one hand, and various gestagens, such as levonorgestrel, desogestrel, 3-ketodesogestrel and gestodene, on the other hand.

For further details for the determination of dose equivalents of various gestagenic active ingredients, reference is made to "Probleme der Dosisfindung: Sexualhormone" [Problems of Dose-Finding: Sex Hormones]; F. Neumann et al. in "Arzneimittelforschung" (Pharmaceutical Agent Research) 27, 2a, 296-318 (1977), as well as to "Aktuelle Entwicklungen in der hormonalen Kontrazeption" [Current Developments in Hormonal Contraception]; JH. Kuhl in Gyn. akologie" [Gynecologist] 25: 231-240 (1992).

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Area with the  $17\beta$ -estradiol level in groups of 30 females, who are treated with an oral contraceptive (75  $\mu\text{g}$

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of gestodene+20  $\mu\text{g}$  of ethinylestradiol) in 21- or 23-day administration interval over three cycles.

FIG. 2: Number of females in %, who showed follicular developments (>13 mm diameter) with 21- or 23-day treatment with an oral contraceptive (75  $\mu\text{g}$  of gestodene+20  $\mu\text{g}$  of ethinylestradiol).

We claim:

1. A combination product for oral contraception, comprising

(a) 23 or 24 dosage units, each containing an estrogen selected from  
>2.0 to 6.0 mg of  $17\beta$ -estradiol and  
0.020 mg of ethinylestradiol;

and a gestagen selected from  
[0.25 to 0.30 mg of] drospirenone and  
[0.1 to 0.2 mg of] cyproterone acetate, in an amount which is equivalent to 75  $\mu\text{g}$  of gestodene.

and

b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units respectively, is to be followed by 5 or 4, respectively pill-free or placebo pill days.

2. A combination preparation for oral contraception according to claim 1, wherein the estrogen is ethinylestradiol.

3. A combination preparation of claim 2, wherein the gestagen is cyproterone acetate.

4. A combination preparation of claim 2, wherein the gestagen is drospirenone.

5. A combination preparation according to claim 1, wherein the estrogen is present in a dose of 20  $\mu\text{g}$  of ethinylestradiol or an equivalent dose of  $17\beta$ -estradiol and the gestagen is present in a dose equivalent to 75  $\mu\text{g}$  of [gestadene] gestodene.

6. A combination preparation according to claim 1, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.

7. A combination preparation according to claim 1, which comprises 23 dosage units, each containing 20  $\mu\text{g}$  of ethinylestradiol and a dose of cyproterone acetate or drospirenone equivalent to 75  $\mu\text{g}$  of gestodene and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.

8. A combination preparation of claim 1, wherein the estrogen is  $17\beta$ -estradiol.

9. A combination preparation of claim 8, wherein the gestagen is cyproterone acetate.

10. A combination preparation of claim 8, wherein the gestagen is drospirenone.

11. A combination preparation of claim 4, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 5 days of the menstrual cycle.

12. A combination preparation of claim 4, which comprises 24 dosage units and 4 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 4 days of the menstrual cycle.

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13. A combination product for oral contraception, comprising

- (a) 23 or 24 daily dosage units, each containing 0.020 mg of ethinylestradiol, and an amount of drospirenone which is equivalent to 75  $\mu$ g of gestodene, and
- (b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units, respectively, is to be followed by 5 or 4, respectively, pill-free or placebo pill days,

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wherein each of the dosage units containing drospirenone contains the same amount of drospirenone.

14. A combination preparation of claim 13, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 5 days of the menstrual cycle.

15. A combination preparation of claim 13, which comprises 24 dosage units and 4 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 4 days of the menstrual cycle.

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